Are memories just ripples in time?

The hippocampus is necessary for the consolidation of long-term episodic memory, and it is also the source of a characteristic electrical phenomenon, the sharp-wave ripples. Researchers are now looking for a possible connection between these two functions in their quest to understand how we form memories. **Michael Gross** reports.

Henry Molaison (1926–2008) suffered from severe epilepsy until 1953, when a surgeon undertook a drastic experimental intervention and removed parts of his brain, including both hippocampi. That operation cured the epilepsy, but it soon became clear that it also gave the patient a new, equally serious disability. The brain surgery blocked Molaison's ability to form new memories and turned him into a textbook example of amnesia, widely known by his initials H.M.

H.M. remained able to recall events he witnessed before the operation (although there was a gradual loss of recollections from the last two years before), but new impressions didn't register permanently, falling into oblivion after 30 seconds. This kind of memory loss is known as anterograde amnesia. Generations of scientists have studied H.M., who would cheerfully carry out the same psychological tests a hundred times, seeing as he didn't remember doing them before. Suzanne Corkin from MIT, who studied his case for decades, has just published a book about his life with amnesia (*Permanent Present Tense: The Man with No Memory, and What He Taught the World*, Allen Lane, London, 2013).

Based on their observations and on animal studies they inspired, researchers concluded that the hippocampus is necessary for the creation and consolidation of long-term episodic memory in the neocortex (see the review by Preston and Eichenbaum on pages R764–R773 of this issue). The episodic memory records sequences of events that we have experienced, including paths that we have travelled. If, for instance, you explain a route that you have taken many times to someone who hasn't, you may recall visual impressions from your episodic memory to supply visual details that may help the novice. In a recent study, B.E. Pfeiffer and D.J. Foster from Johns Hopkins University at Baltimore, Maryland, USA, have shown that hippocampal sequences observed in performing rodents seem to be linked to route planning, inasmuch as they allow researchers to predict which path the animals will take (Nature (2013) *497*, 74–79).

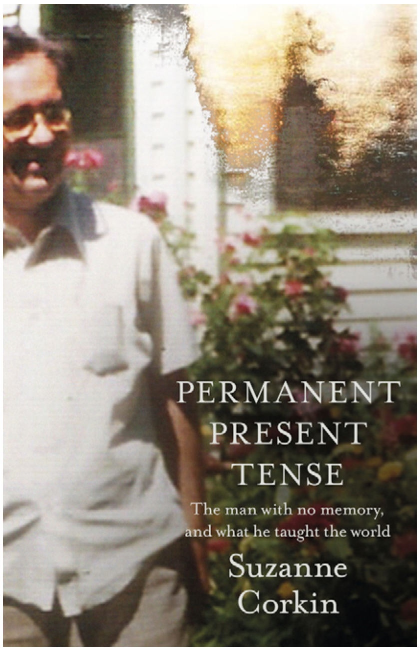
This kind of memory is entirely separate from procedural memory, which covers learned motor skills, such as riding a bicycle. After his surgery, H.M. was still able to learn new motor skills, though he couldn't remember learning them.

Picking impulses apart

But how does the hippocampus coordinate the storage of episodic memories in the cortex? One hypothesis links a unique kind of fast electrical oscillations, known as ripples, to the consolidation and replay of such memories. John O'Keefe and Lynn Nadel first reported the existence of ripples in the 1970s. Further work by researchers such as György Buzsaki advanced their characterization and electrophysiological mechanism, and in 2007 the McNaughton-Barnes group provided preliminary evidence that such patterns exist in nonhuman primates. Nikolai Axmacher in Bonn and others showed that ripples can be found also in humans. However, a solid mechanism for a role of ripples in memory processes remains to be established, and some researchers doubt that oscillations are needed for memory function.

These ripples have variable frequencies and don't last longer than a tenth of a second overall. Typically, they arise in the hippocampus at resting times, when there is no new information to be processed. A current hypothesis is that the hippocampus uses 'offline' time to replay recent impressions and consolidate them in the long-term memory with the help of these ripples.

With rodents learning the path through a maze, researchers have established direct connections between ripples and learning success. Over the last few years, new techniques have enabled scientists to tease apart which cells contribute impulses to the ripple and which other cells are tuned to pick up the signals conveyed by them.

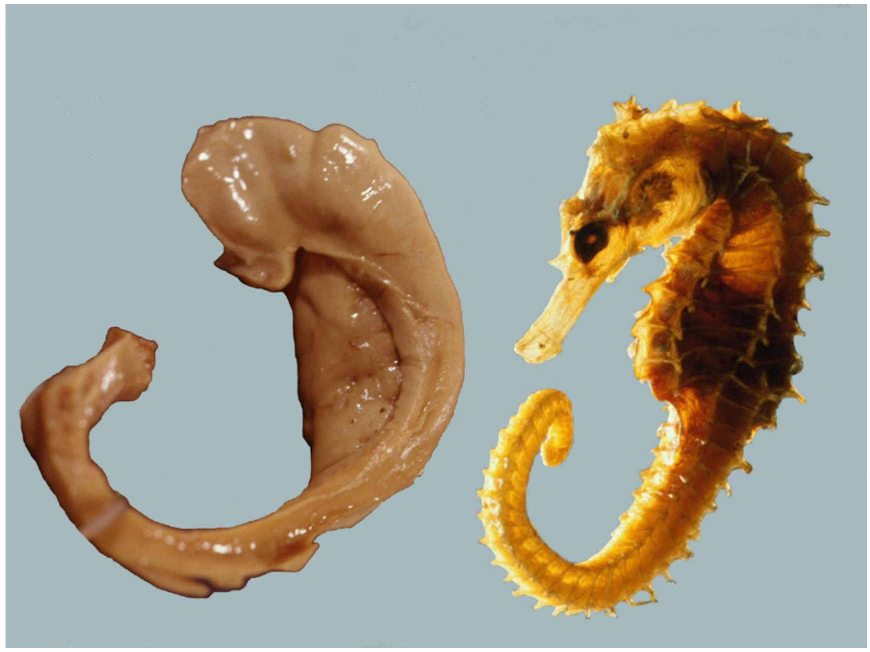


Present tense: The case of H.M., a patient who lost the ability to record new memories after removal of his hippocampi, provided key insights into the importance of the hippocampus for memory and is the focus of a new book by Suzanne Corkin. (Photo: courtesy of Allen Lane Publishers.)

Nicolas Maier and colleagues at the Charité hospital in Berlin developed a set of methods to measure ripples in thin slices of rodent brains from the perspective of a single recipient cell. With this method, graduate student Álvaro Tejero-Cantero from the Ludwigs Maximilian University of Munich analysed which excitatory and inhibitory signals the pyramidal cells in the CA1 region of the hippocampus perceive during a ripples event.

Pyramidal cells are of particular interest in this context, as groups of such cells are believed to represent spatial memories and they form connections to other parts of the brain. Tejero-Cantero and others could show that these pyramidal cells produce electrical impulses that are coordinated with the ripples they detect. Tejero-Cantero also developed an algorithm enabling him to pick apart the various impulses that a given pyramidal cell receives and to record their arrival time with high precision. Charting the arrival times of many impulses, he discovered that excitation and inhibition, which were alternating in the beginning of a ripple event, changed their phase behaviour and ended up coinciding and thus cancelling each other (Neuron (2011) *72*, 137–152). From this, Tejero-Cantero, who now works at Oxford University, concludes that the inhibitory impulses are necessary to limit the timeframe of the ripples.

For each separate recollection of our episodic memory, many pyramidal cells have to be activated simultaneously by the same ripple event. Together with Axel Kammerer and Christian Leibold, Tejero-Cantero modelled the properties that the network of these pyramidal cells needs to function. Apart from suggesting optimal numbers of cells and connections, the model also showed, in agreement with the experimental results described above, that the use of inhibitory pulses along with excitatory ones helps to improve the capacity of the network (J. Comput. Neurosci. (2013) *34*, 125–136).



Sea horses: The hippocampus, a small brain structure named after its similarity to sea horses. Humans have two hippocampi, which are located in the medial temporal lobes. It is known to have a crucial role in the recording and replay of episodic memory, but the precise mechanisms of this function have remained elusive. (Photo: Wikipedia, Professor Laszlo Seress.)

Ripples around the brain

These investigations only cover the effects the ripples have within the hippocampus, but if they really consolidate memories elsewhere in the brain, their interactions with other brain areas must also be investigated. The group of Nikos Logothetis at the Max-Planck Institute for Biological Cybernetics at Tübingen, Germany, has for the first time combined electrophysiological measurements of ripple events with magnetic resonance imaging (MRI). Specifically, the group developed a new methodology they call neural-event-triggered functional magnetic resonance or NET-fMRI to examine the spatial embeddedness of local brain patterns defined beforehand (Nature (2012) *491*, 547–553). As György Buzsaki and Adrien Peyrache summarised in a highlight article (Trends Cogn. Sci. (2012) *17*, 57–59): “The idea behind this study is simple: the authors selected an electrophysiologically well-characterized brain pattern as a seed and examined the metabolic state of nearly the entire brain surrounding that event.”

Applying this approach to the hippocampal ripples and measuring the blood-oxygen level dependent (BOLD) fMRI signal, the researchers could show that large parts of the cortex — but not the visual cortex — are activated during ripple events, while other parts of the brain, such as the brainstem and the midbrain, are inhibited.

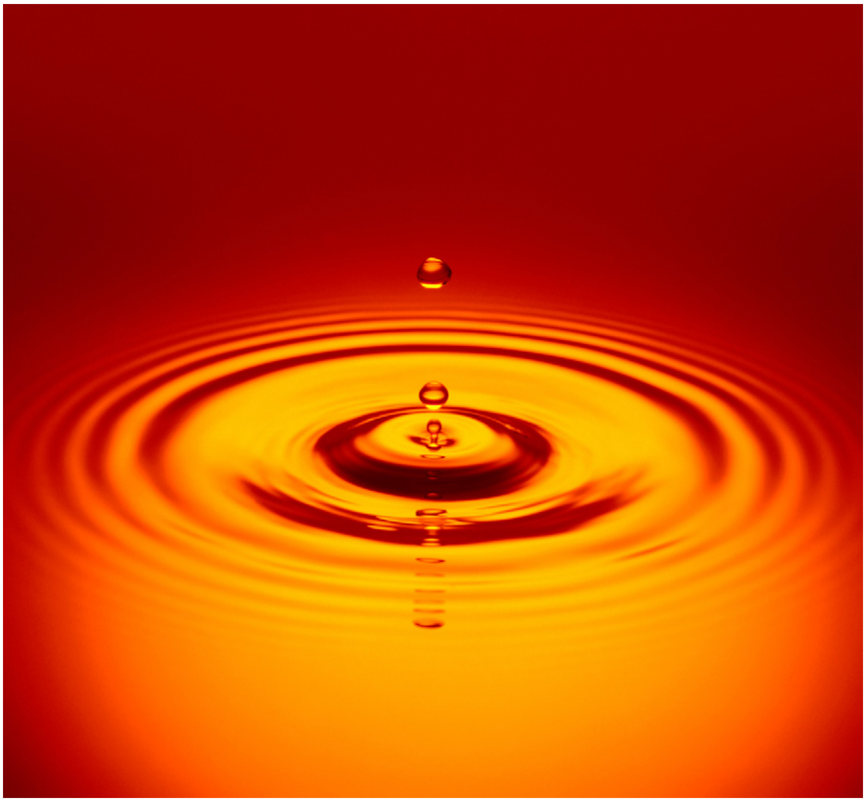
This large-scale pattern of excitation and inhibition, combined with the timecourse of events observed, seems to suggest that, during the consolidation of memories, the access routes for new impressions are briefly shut down, allowing the brain to focus on replaying and immortalising the memories. Logothetis warns against interpreting the recorded timecourse of events as a chain of cause–effect relationships, and points to the complexity of the underlying dynamics. In the Nature paper, the authors conclude that “events in isolation are likely to be indicators rather than effectors of any cognitive capacity.”

As we use electromagnetic waves in communication technology all the time, it is very tempting to interpret these ripples in terms of broadcasting technology, thinking of signals that are sent and received, and trigger actions. However, Logothetis warns that such metaphors may be misleading, suggesting that ripples should best be seen as markers. “They are transient oscillations that extremely precisely synchronise hippocampal neurons to fire all together in the same spatial and temporal order they did during the acquisition of knowledge,” he explains. “Such ‘super-sync’ firing is extremely powerful for inducing plasticity changes in the target regions. In fact, ripples are ‘release’ phenomena, in the sense that the whole state of the system becomes such that the strong inhibitory effects of medial septum are transiently reduced.”

As with previous technology metaphors from clockwork through to computers, our attempts to describe the brain with reference to machinery we can build must ultimately fail as we are unable to build anything as complex as a human brain.

Applications and outlook

Progress in understanding how memories are established in the brain raises the prospect of manipulating them. This possibility has so far mainly been explored in movies, such as *Eternal Sunshine of the Spotless Mind*, where protagonists undergo



Ripple effect: Short bursts of electrical impulses known as sharp-wave ripples may, according to one hypothesis, be the key to the function of the hippocampus in consolidating memories.

a procedure to have memories associated with ex-lovers erased, but there are very real medical applications in treatment of trauma disorders that could benefit from such options. However, the misuse potential is considerable and should also be taken into account.

Another conceivable manipulation of memory is the production of false associations. In a recent paper, the group of Susumu Tonegawa at MIT used optogenetic methods based on channelrhodopsin labelling (Curr. Biol. (2011) *21*, R831–R833) to create a fear conditioning in mice that was not based on real events experienced by the animals (Science (2013) *341*, 387–389). Specifically, the researchers targeted either the dentate gyrus (DG) or the CA1 region of the hippocampus, labelled the neurons active in one situation (context A) and then optically re-activated them during a fear-conditioning experiment in a different situation (context B). When they were exposed to context A again, the animals had a fear reaction, i.e. freezing behaviour, even though this context was never associated with the feared stimulus. Remarkably, this manipulation succeeded when it was applied to the DG, but not in the CA1 region. At this stage, it is unclear why the CA1 did not produce a false association.

All this exciting research hasn't been much use for H.M., who has helped science much more than science could ever help him. Since his death in 2008, Molaison has continued to make valuable contributions to neuroscience. A unique neuroanatomical project chaired by Jacopo Annese at the Brain Observatory, University of California at San Diego, investigates slices of his brain in great detail with a view of establishing precisely which anatomical changes were producing his symptoms. Ironically, although H.M. couldn't remember a single thing that happened after 1953, his memory will stay with us for many years.

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Essay

Cultural memory

Humans have a form of externalised memory. They are able to transmit information across generations in the form of learned cultural traditions and preserve this knowledge in artefacts. How this capability evolved from the simpler traditions of other animals is an active area of research.

Kevin N. Laland* and Luke Rendell

Memory is a wonderful resource that allows individual animals to walk around with a store of relevant past experience in their brains. We not only remember those childhood games, or past events like our wedding or a sporting success, but we also file away legions of prosaic practical advice — how to drive, how to cook, how to work the TV remote — which we draw on when needed. There are other kinds of memory too. For instance, natural selection creates a genetic memory of organismal characters that proved successful in promoting survival and reproduction in ancestral environments. Likewise, human societies today benefit from extraordinary cultural memories — vast domains of information far beyond the capacity of a single human brain, banked in an array of different stores (Figure 1), from artefacts and constructed environments, through to libraries and the World Wide Web. Our very success as a species is undoubtedly in part attributable to our uniquely huge distributed memory store of cultural knowledge.

While cultural inheritance has long been recognized as important to human biology, recent research reveals that the social transmission of learned knowledge is widespread in animals, not just in vertebrates, but also in invertebrates. All sorts of creatures learn valuable life skills, such as what to eat, where to find it, how to process it, what a predator looks like, how to escape that predator, how to move safely through the environment, whom to mate with, and so forth, by observing and copying other animals. Inexperienced female fruit flies, for instance, copy the mate-choice decisions of other